Applicant	:	Kenneth Weisman and Michael E. Goldberg
Invention	:	METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS

This is a patent application of which includes the following:

1. Transmittal letter in duplicate
2. Specification - 6 pages
3. 14 Claims - 3 pages
4. Abstract of Disclosure - 1 page
5. Declaration for Patent Application
6. Verified Statement Claiming Small Entity Status (37 CFR 1.9(f) and 1.27(b))- Independent Inventor
7. Return Receipt Postcard

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Date of Deposit: June 3, 1998

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André Steed

Andre Steed

Docket Number (Optional)

PATENT APPLICATION TRANSMITTAL LETTER W1068/20011

To the Commissioner of Patents and Trademarks:
Transmitted herewith for filing under 35 U.S.C. 111 and 37 CFR 1.53 is the patent application of
Kenneth Weisman and Michael E. Goldberg

entitled METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS

Enclosed are:

☒ 10 pages of written description, claims and abstract.
☐ 0 sheets of drawings.
☐ an assignment of the invention to _____
☒ executed declaration of the inventors.
☐ a certified copy of a _____ application.
☐ associate power of attorney.
☒ a verified statement to establish small entity status under 37 CFR 1.9 and 1.27. - Independent Inventor.
☐ information disclosure statement
☐ preliminary amendment
☐ other: _____

CLAIMS AS FILED

	NUMBER FILED	NUMBER EXTRA	RATE	FEE
BASIC FEE	[ ]		$790	$790
TOTAL CLAIMS	[14 - 20 =]	0	x22	$ 0
INDEPENDENT CLAIMS	[5 - 3 =]	2	x82	$164
MULTIPLE DEPENDENT CLAIM PRESENT	[ ]		$720	
* NUMBER EXTRA MUST BE ZERO OR LARGER		]	TOTAL	$ 954

If applicant has small entity status under 37 CFR 1.9 and 1 27, then divide total fee by 2, and enter amount here.	SMALL ENTITY TOTAL	$ 477

☐ A check in the amount $ _____ to cover the filing fee is enclosed.
☒ The Commissioner is hereby authorized to charge and credit Deposit Account No. 03-0075 as described below, I have enclosed a duplicate copy of this sheet.
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- ☐ Charge the issue fee set in 37 CFR 1.18 at the mailing of the Notice of Allowance, pursuant to 37 CFR (1.311(b).

June 3, 1998
Date

Signature

Alan H. Bernstein
Typed or printed name

Caesar, Rivise Bernstein, Cohen & Pokotilow, Ltd.
12th Floor, Seven Penn Center, 1635 Market Street
Philadelphia, PA 19103-2212 Phone 215-567-2010

PATENT

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE
APPLICATION FOR LETTERS PATENT

APPLICANTS	:	Kenneth Weisman and Michael E. Goldberg
POST OFFICE ADDRESS	:	30 Springton Pointe Drive Newtown Square, PA 19073 20 Aspen Drive Ivyland, PA 18974
INVENTION	:	METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS
ATTORNEYS	:	Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd. 1635 Market Street Philadelphia, PA 19103-2212

TO ALL WHOM IT MAY CONCERN:

Be it known that we, Kenneth M. Weisman and Michael E. Goldberg, citizens of the United States of America, residing above, have made a certain new and useful invention as set forth above of which the following is a specification.

This application claims the benefit of the filing dates of Provisional Patent Applications Serial No. 60/049,003 (filing date June 9, 1997); 60/049,160 (filing date June 9, 1997); 60/049,746 (filing date June 12, 1998); 60/049,162 (filing date June 9, 1997); 60/049,169 (filing date June 9, 1997); 60/041,070 (filing date March 18, 1997).

BACKGROUND OF THE INVENTION

There are many steps in the biosynthesis and utilization by the tissues of testosterone. Testosterone is made mostly in the testicles. A lesser amount is made in the adrenals. Production is stimulated by secretion of Gn RH or LHRH by the brain, which causes secretion of luteinizing hormone (LH) by the pituitary, which causes the testicles to make testosterone. Testosterone then flows into the blood stream and is absorbed by the target cells. Here it binds to a receptor and is transported into the cell and converted to dihydrotestosterone. This is bound and carried to the nucleus of the cell where it redirects cellular activity by turning on and off DNA. Hormonal manipulation is a term which refers to the reduction of testosterone or its effects by blocking any step in the above process in order to gain a desired effect. Until now the uses of hormonal manipulation include for example treating prostatic carcinoma, and treatment for baldness.

The present invention involves the use of hormonal manipulations in the prevention and treatment of atherosclerosis, coronary heart disease, stroke and peripheral vascular disease.

Leuprolide acetate is a synthetic nonapeptide of naturally occurring gonadotropin-releasing hormone (GnRH or LH-RH), the chemical name is 5-oxo-L-prolyl-L-histidyl-L-tryptophyl-L-seryl-L-tyrosyl-D-leucyl-L-leucyl-L-arginyl-N-ethyl-L-prolinamide acetate salt sold under the trade name Lupron or Lupron Depot, as identified by US patent no. 4,897,256, the entire disclosure is incorporated by

reference herein, is known for use in the treatment of prostatic carcinoma. Leuprolide is a potent inhibitor of gonadotropin secretion known to decrease levels of LHRH, LH and Testosterone.

Goserelin Acetate, a synthetic decapeptide analogue of LHRH or GnRH, is chemically described as an acetate salt of [D-Ser(Bu^t)^6 Azygly^{10}] LHRH. Its chemical structure is pyro-Glu-His-Trp-Ser-Tyr-D-Ser(Bu)-Leu-Arg-Pro-Azgly-NH2 acetate [C59H84N18014 (C2H4O2) sold under the trade name Zoladex, as identified by the US patent no. 5,510,460, the entire disclosure is incorporated by reference herein, is known for the use in treatment of prostatic carcinoma. Goserelin acetate is a potent inhibitor of gonadotropin secretion known to reduce levels of GnRH or LHRH, LH and Testosterone.

Nilutamide, a nonsteroidal, orally active, antiandrogen, having the chemical name 5,5-dimethyl 3-[4-nitro-3-(trifluoromethyl)phenyl] 2,3-imidazolidinedlone, sold under the trade name Nilandron, as identified by US patent no. 5,023,088, the entire disclosure is incorporated by reference herein, is known for use in treatment of prostatic carcinoma.

Flutamide, an acetanilid, nonsteroidal androgen having the chemical name, 2-methyl-N-[4-nitro-3-(trifluoromethyl)phenyl] propanamide sold under the trade name Eulexin, as identified by US patent nos. 3,995,060 and 4,474,813, the entire disclosure of which are incorporated by reference herein, Flutamide is known for use in treatment of prostatic carcinoma.

Bicalutamide, a non-steroidal antiandrogen, chemical name is propanamide, N-(4 cyano-3-(trifluoromethyl)phenyl]-3-[(4-fluorophenyl)sulfonyl]-2-hydroxy-2-methyl-(+-) sold under the trade name Casodex, as identified by US patent no. 4,636,505, the entire disclosure is incorporated by reference herein, is known for use in treatment of prostatic carcinoma.

A retrospective study was performed which compared the rates of patient reported heart attack in several groups: 1 - control group of males entering the urology office for any routine complaint. 2 - a group of prostate cancer patients treated with Leuprolide acetate, a LHRH inhibitor. 3 - a group of prostate cancer patients treated with Goserelin acetate (Zoladex), a LHRH inhibitor. 4 - a group of prostate cancer patients not treated with hormonal manipulation (neither Leuprolide or Goserelin). 5 - a group of patients treated with Finasteride (another form of hormonal manipulation). 6 - all patients on LHRH inhibitors (group 2 + group 3).

The patients on either Leuprolide or Goserelin were treated with the recommended doses indicated for the treatment of prostatic carcinoma, at either one or three month intervals depending on the preparation used. Leuprolide was dosed at 7.5 mg monthly (single intramuscular injection) or at 22.5 mg at 3 month intervals (single intramuscular injection). Goserelin was dosed at 3.6 mg monthly (subcutaneous injection) or at a dose of 10.8 mg at 3 month intervals (subcutaneous injection).

The various groups of office patients were given a questionnaire. In groups 2, 3 and 5 only those on drug for at least one year were considered. Cardiac event is defined as either the history of a heart attack or occurrence of coronary artery bypass or angioplasty. In control groups only events occurring in the 3 years prior to the questionnaire are charted. The results were as follows:

	No Patients	Cardiac Events	Subject Years	Events/Year
Group 1 (control no cancer)	247	26	741	.0351
Group 4 (control cancer patients)	69	6	207	.0290
Total Control (Groups 1 + 4)	316	32	948	.0338
Group 2 (Lupron)	28	1	118	.00847
Group 3 (Zoladex)	25	1	62	.0161
Group 5 - (Finasteride)	91	4	242	.0165
Group 6 (antiLHRH) groups 2 + 3	50	2	180	.0111

The observed difference between the proportions of Total Control vs Group 6 (LHRH) is .0226. 95% Confidence Interval for the difference between the proportions is .00350 to .0418. Patients treated with LHRH inhibitors had fewer heart attacks than controls.

The observed difference between the proportions of Group 2 (Lupron) and Total Control is .0253. 95% Confidence Interval for the difference between the proportions is .00514 and .0454. Patients treated with Leuprolide acetate had fewer heart attacks than controls.

The observed difference between the proportions of Group 3 and Total Control is .0177. Patients treated with Goserelin (Zoladex) had fewer heart attacks than controls.

The observed difference between the proportions of Group 1 (Control) and Group 5 (Finasteride) is .0186. 90% Confidence Interval for the difference between the proportions is .00103 to .0361. Patients treated with Finasteride had fewer heart attacks than control.

Without further elaboration the foregoing will so fully illustrate our invention that others may, by applying current and future knowledge, adopt the same for use under various conditions of service.

CLAIMS

1. A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease comprising administering to an animal or human an amount of a substance which acts to decrease the levels of testosterone or which inhibits the actions of testosterone.

2. A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease comprising administering to a human or an animal an amount of a substance which is an inhibitor of the release of LHRH or GnRH, or any substance which inhibits the action or effects of LHRH, resulting in decreased levels of LH (luteinizing hormone).

3. A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease comprising administering to an animal or human an amount of Finasteride or other inhibitor of 5 alpha reductase inhibitor or an inhibitor of any subtype of that enzyme resulting in decreased levels of dihydrotestosterone (DHT), in an amount sufficient to reduce atherosclerosis.

4. A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease

comprising administering to an animal or human an amount of non-steroidal antiandrogen sufficient to reduce atherosclerosis.

5. The method of Claim 4 comprising administering to a human or an animal an amount of Bicalutamide sufficient to reduce atherosclerosis.

6. The method of Claim 5 wherein the effective amount of Bicalutamide is 50 mg as an oral tablet taken daily.

7. The method of Claim 5 wherein Bicalutamide is administered as a tablet, or as part of a liquid solution or dispersion, or patch, or subcutaneous pellet, or intramuscular injection, or any other method with the intent of accomplishing systemic absorption of the drug sufficient to reduce atherosclerosis.

8. The method of Claim 4 comprising administering to a human or an animal an amount of Flutamide sufficient to reduce atherosclerosis.

9. The method of Claim 8 wherein the effective amount of Flutamide is 250 mg orally three times a day.

10. The method of Claim 5 wherein Flutamide is administered as a tablet, or as part of a liquid solution or dispersion, or patch, or subcutaneous pellet, or intramuscular injection, or any other method with the intent of accomplishing systemic absorption of the drug sufficient to reduce atherosclerosis.

11. The method of Claim 4 comprising administering to a human or an animal an amount of Nilutamide sufficient to reduce atherosclerosis.

12. The method of Claim 11 wherein the effective amount of Nilutamide is 50 mg orally three times a day.

13. The method of Claim 11 wherein Nilutamide is administered as a tablet, or as part of a liquid solution or dispersion, or patch, or subcutaneous pellet, or intramuscular injection, or any other method with the intent of accomplishing systemic absorption of the drug sufficient to reduce atherosclerosis.

14. A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease comprising administering to an animal or human an amount of a substance sufficient to decrease or inhibit synthesis of testosterone.

ABSTRACT OF DISCLOSURE

A method of decreasing atherosclerosis and its complications including but not limited to myocardial infarction, stroke and peripheral vascular disease wherein the method involves administering to a human or an animal an amount of a substance sufficient to reduce atherosclerosis.

DECLARATION FOR PATENT APPLICATION

Docket No. W1068/20011

As a below named inventor, I hereby declare that:

My residence, post office address and citizenship are as stated below next to my name.

I believe I am the original, first and sole inventor (if only one name is listed below) or an original, first and joint inventor (if plural names are listed below) of the subject matter which is claimed and for which a patent is sought on the invention entitled

METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS

the specification of which is attached hereto unless the following box is checked:

☐ Was filed on _____ as United States Application Number or PCT International Application Number _____ and was amended on _____ (if applicable).

I hereby state that I have reviewed and understand the contents of the above identified specification, including the claims, as amended by any amendment referred to above.

I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56. I hereby claim foreign priority benefits under 35 U.S.C. §119(a)-(d) or § 365(b) of any foreign application(s) for patent or inventor's certificate, or § 365(a) of any PCT International application which designated at least one country other than the United States, listed below and have also identified below, by checking the box, any foreign application for patent or inventor's certificate, or PCT International application having a filing date before that of the application on which priority is claimed.

Prior Foreign Application(s)			Priority Not Claimed
NONE			☐
(Number)	(Country)	(Day/Month/Year Filed)	
			☐
(Number)	(Country)	(Day/Month/Year Filed)	

I hereby claim the benefit under 35 U.S.C. §119(e) of any United States provisional application(s) listed below.

NONE	
(Application Number)	(Filing Date)
(Application Number)	(Filing Date)

I hereby claim the benefit under 35 U.S.C. § 120 of any United States application(s), or § 365(c) of any PCT International application designating the United States, listed below and, insofar as the subject matter of each of the claims of this application is not disclosed in the prior United States or PCT International application in the manner provided by the first paragraph of 35 U.S.C. § 112, I acknowledge the duty to disclose information which is material to patentability as defined in 37 CFR §1.56 which became available between the filing date of the prior application and the national or PCT International filing date of this application.

NONE		
(Application Number)	(Filing Date)	(Status-patented, pending, abandoned)
(Application Number)	(Filing Date)	(Status-patented, pending, abandoned)

I hereby appoint the following attorney(s) and/or agent(s) to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith:

Alan H. Bernstein (Registration No. 19,315); Stanley H. Cohen (Registration No. 20,235); Manny D. Pokotilow (Registration No. 22,492); Barry A. Stein (Registration No. 25,257); Martin L. Faigus (Registration No. 24,364); Eric S. Marzluf (Registration No. 27,454); Robert S. Silver (Registration No. 35,681); Scott M. Slomowitz (Registration No. 39,032); Michael J. Berkowitz (Registration No. 39,607) and David M. Tener (Registration No. 37,054) care of Caesar, Rivise, Bernstein, Cohen & Pokotilow, Ltd., 12th Floor, Seven Penn Center, 1635 Market Street, Philadelphia, Pennsylvania 19103-2212, my attorneys with full power of substitution and revocation, to prosecute this application and to transact all business in the Patent and Trademark Office connected therewith.

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under Section 1001 of Title 18 of the United States Code and that such willful false statements may jeopardize the validity of the application or any patent issued thereon.

Full name of sole or first inventor (given name, family name) Kenneth M. Weisman

Inventor's signature Kenneth M. Weisman Date 5/31/98

Residence 30 Springton Pointe Drive, Newtown Square, PA 19073 Citizenship USA

Post Office Address

Full name of second joint inventor, if any (given name, family name) Michael Goldberg

Second Inventor's signature Date 6/1/98

Residence 20 Aspen Drive, Ivyland, PA 18974 Citizenship USA

Post Office Address

☐ Additional Inventors are being named on separately numbered sheets attached hereto.

VERIFIED STATEMENT CLAIMING SMALL ENTITY STATUS (37 CFR 1.9(f) & 1.27(b))--INDEPENDENT INVENTOR	Docket Number (Optional) W1068/20011

Applicant or Patentee: Kenneth M. Weisman and Michael Goldberg

Serial or Patent No.: _____

Filed or Issued: _____

Title: METHOD OF DECREASING ATHEROSCLEROSIS AND ITS COMPLICATIONS

As a below named inventor, I hereby declare that I qualify as an independent inventor as defined in 37 CFR 1.9(c) for purposes of paying reduced fees to the Patent and Trademark Office described in:

[X] the specification filed herewith with title as listed above.

[ ] the application identified above.

[ ] the patent identified above.

I have not assigned, granted, conveyed or licensed and am under no obligation under contract or law to assign, grant, convey or license, any rights in the invention to any person who would not qualify as an independent inventor under 37 CFR 1.9(c) if that person had made the invention, or to any concern which would not qualify as a small business concern under 37 CFR 1.9(d) or a nonprofit organization under 37 CFR 1.9(e).

Each person, concern or organization to which I have assigned, granted, conveyed, or licensed or am under an obligation under contract or law to assign, grant, convey, or license any rights in the invention is listed below:

[X] No such person, concern, or organization exists.

[ ] Each such person, concern or organization is listed below.

Separate verified statements are required from each named person, concern or organization having rights to the invention averring to their status as small entities. (37 CFR 1.27)

I acknowledge the duty to file, in this application or patent, notification of any change in status resulting in loss of entitlement to small entity status prior to paying, or at the time of paying, the earliest of the issue fee or any maintenance fee due after the date on which status as a small entity is no longer appropriate. (37 CFR 1.28(b))

I hereby declare that all statements made herein of my own knowledge are true and that all statements made on information and belief are believed to be true; and further that these statements were made with the knowledge that willful false statements and the like so made are punishable by fine or imprisonment, or both, under section 1001 of Title 18 of the United States Code, and that such willful false statements may jeopardize the validity of the application, any patent issuing thereon, or any patent to which this verified statement is directed.

Ken Weisman	Michael Goldberg	
NAME OF INVENTOR	NAME OF INVENTOR	NAME OF INVENTOR
Kenneth Weisman		
Signature of inventor:	Signature of inventor:	Signature of inventor:
5/31/98	6/1/98	
Date	Date:	Date:

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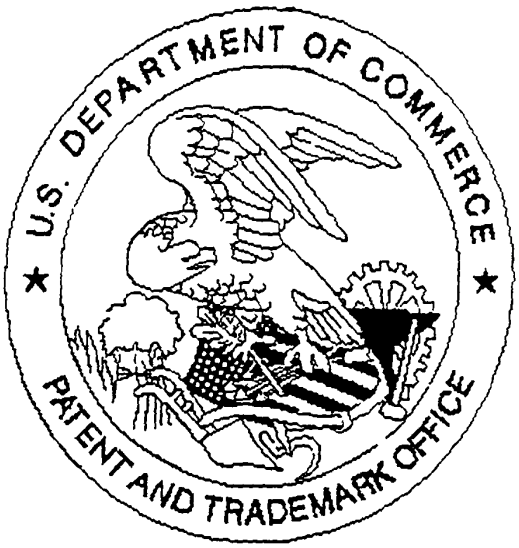

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